

Second Primary Neoplasms Following Ovarian Cancer¹

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ABSTRACT—Follow-up surveys of patients with ovarian cancer revealed an increased risk of second primary cancers of the uterine corpus, colon, bladder, breast, and hematopoietic system. The excess risk of uterine corpus cancer was independent of therapy. The risk of colon cancer was increased in all treatment groups but was especially high among patients receiving radiation or chemotherapy. The predisposition to other neoplasms was limited to certain treatment groups: bladder cancer to irradiation, leukemia to chemotherapy, and lymphoma to either modality. The pattern of second neoplasms following ovarian cancer appears to be influenced by therapy as well as by common etiologic factors.—*J Natl Cancer Inst* 61:1195-1197, 1978.

Ovarian carcinoma is the fifth most common fatal cancer among women in the United States (1). Previous surveys of patients with this tumor have indicated an excess risk of subsequent primary cancers of the colon, endometrium, and perhaps breast (2, 3). This constellation of tumors may result from common etiologic influences, but the carcinogenic effects of therapy for ovarian cancer have not been evaluated. The use of alkylating agents and radiation for ovarian cancer has resulted in a number of women at risk of late complications. To evaluate the patterns of second cancers that may complicate ovarian carcinoma, follow-up surveys were made of 2 groups of patients: those registered with the E.R.P. of the NCI and those identified by a survey of 70 medical centers using alkylating agents for treatment of this tumor.

METHODS

E.R.P.—The E.R.P. of the NCI (4) provided data on 13,309 women with the diagnosis of ovarian cancer of all clinical stages and histologic types from 1935 through 1972. Information was available on race, age at diagnosis, initial and subsequent modes of therapy (surgery, radiation, chemotherapy, and hormone therapy), status at annual follow-up examination, and development of new primary cancers.

Age- and time-specific person-years of survival were tabulated from the diagnosis of ovarian cancer to the diagnosis of a second primary cancer, date of death, or closing date of the study (December 1971), whichever came first. Persons lost to follow-up (7%) were included in the analyses and considered at risk of developing a second cancer until the middle of the year in which the patients were last known to be alive.

We calculated the expected numbers of cancers by applying the age-, sex-, and time-specific incidence rates from the general population to the corresponding person-years of follow-up in the patients with ovarian cancer. The rates used were from the Connecticut Tumor Registry (5, 6). Inasmuch as 37% of the patients in the E.R.P. came from Connecticut hospitals, this seemed an appropriate comparison group.

Current survey.—We canvassed members of the Society of Gynecologic Oncologists representing 70 institutions involved in the study of alkylating agent therapy in advanced ovarian carcinoma. We requested information on the number of patients with ovarian cancer treated at each institution from 1970 through 1975, on the percentage receiving chemotherapy, and on all patients with second primary neoplasms. Representatives of 51 of these institutions (73%) agreed to participate in the study and contributed data on 5,455 patients with ovarian cancer. Sixteen of the centers, accounting for 1,704 patients, supplied data on the percentage treated with chemotherapy (80%).

We calculated the expected numbers of second cancers in this current survey by applying the age- and sex-specific incidence rates obtained in the Third National Cancer Survey, 1969-71 (7) to the number of person-years at risk. Survival was estimated by the age-specific survival experiences of the E.R.P. series.

Data on person-years at risk were given by follow-up interval during 1970-75 but were not always synonymous with survival because the entry date of the study for each patient was the first time a patient was treated at the participating institution after 1970.

The strength of association was measured by the exact 95% CI around the ratio of observed to expected cases, referred to as the RR (8). If the lower limit of the CI was greater than 1.0, the RR was considered statistically significant at the 5% level ($P < 0.05$).

RESULTS

End Results Program

The 13,309 patients in this survey were followed for

ABBREVIATIONS USED: CI=confidence interval; E.R.P.=End Results Program; NCI=National Cancer Institute; RR=relative risk(s).

¹ Received March 10, 1978; accepted July 3, 1978.

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⁶ We thank the members of the Society of Gynecologic Oncologists whose cooperative efforts made this study possible; Dr. Max H. Myers for providing data from the End Results Program; and Ms. Terry Thomas, Ms. Nancy Jones, Ms. Wendy Cohen, Ms. Rita Feran, Mrs. Kathy Diblazio, and Ms. Diane Crouse for technical assistance.

45,903 person-years (mean, $3\frac{1}{2}$ yr/person); 2,989 women were followed over 5 years. The average age at diagnosis was 56 years, and the average year of diagnosis and entry into the system was 1958. Radiation was given to 6,596 of these patients (49.6%) as part of their primary treatment. Chemotherapy was used in 2,612 patients (20% of the total), but only 441 were treated during the period covered by the current survey (1970-75); by design of the E.R.P., these patients were followed only through 1972. Information on specific drugs was not stored in the E.R.P. file.

Second primary neoplasms (excluding contralateral ovarian cancer) developed in 364 patients in the total E.R.P. group, compared to 282 cases expected ($RR=1.4$, 95% $CI=1.3-1.6$). Over 96% of second cancers were confirmed histologically. As shown in table 1, the irradiated patients had 185 second cancers, compared to 126 cases expected ($RR=1.5$, 95% $CI=1.3-1.7$). The nonirradiated patients had 179 second cancers, compared to 156 cases expected ($RR=1.1$, 95% $CI=1.0-1.3$). Table 1 gives the relative risks for selected tumors occurring in irradiated versus nonirradiated groups; table 2 lists the risks according to follow-up intervals.

In both treatment groups, the risk was greatest for cancer of the uterine corpus, especially in the first 2 years of follow-up. However, because surgical treatment of ovarian cancer often includes hysterectomy, the expected number of cases for long-term survivors may be an overestimate.

An excess of cancer of the colon (but not rectum) also occurred in both groups but was highest in irradiated patients, particularly those followed 5 years or longer.

The risks of lymphoma and bladder cancer were significantly high only in the irradiated group and did not vary with duration of follow-up. Irradiated patients also had an excess of soft tissue sarcomas, a finding of borderline significance. All 3 connective tissue tumors occurred on the trunk, but whether any arose in the field of irradiation is uncertain. No excess of leukemia or breast cancer was found in either treatment group.

TABLE 2.—*RR of second tumors after ovarian cancer by duration follow-up*

Patients and second tumors	Duration of follow-up ^a			
	<2 yr	2-4 yr	5-9 yr	>9 yr
Previously irradiated patients with:				
Endometrial cancer	10.2 (46)	1.9 (5)	1.9 (5)	— (0)
Colon cancer	3.1 (18)	0.6 (2)	1.4 (5)	2.1 (8)
Bladder cancer	2.8 (5)	2.8 (5)	2.9 (2)	2.9 (2)
Lymphoma	3.1 (4)	3.1 (4)	2.0 (1)	2.0 (1)
Nonirradiated patients with:				
Endometrial cancer	8.1 (34)	0.7 (2)	0.3 (1)	0.9 (3)
Colon cancer	3.0 (20)	0.6 (3)	0.5 (3)	0.6 (4)
Bladder cancer	— (0)	— (0)	0.9 (1)	0.8 (1)
Lymphoma	1.7 (3)	1.7 (3)	2.5 (2)	1.1 (1)

^a Numbers in parentheses are observed No. of instances.

Current Survey

Among 5,455 patients with ovarian cancer, second primary neoplasms were reported in 130 patients compared to 61 cases expected ($RR=2.1$, 95% $CI=1.8-2.5$). As shown in table 1, the risk was highest for leukemia. In an earlier report (9), this risk was determined to be greatest for acute nonlymphocytic leukemia among women followed at least 2 years after alkylating agent therapy ($RR=171.4$, 95% $CI=88.5-299.5$). All 13 leukemia patients received chemotherapy, and 9 had prior radiation therapy.

In addition, this group of patients with ovarian cancer was prone to lymphoma and cancers of the endometrium, colon (but not rectum), and breast (table 1). However, information on survival and prior treatment of these patients was not available. We found no increased risk for bladder cancer or soft tissue sarcomas.

DISCUSSION

Surveys of multiple primary cancers are often handicapped by variable reporting practices of physicians

TABLE 1.—*Second primary cancers after ovarian carcinoma*

Site of second primary cancer	Nonirradiated patients; total, 6,713			Irradiated patients; total, 6,596			Current survey; total, 5,455		
	O/E ^a	RR	95% CI ^b	O/E ^a	RR	95% CI ^b	O/E ^b	RR	95% CI ^b
All sites	179/156	1.1 ^c	1.0-1.3	185/126	1.5 ^c	1.3-1.7	130/61	2.1 ^c	1.8-2.5
Endometrium	40/13.6	2.9 ^c	2.1-4.0	56/12.4	4.5 ^c	3.4-5.9	30/5.1	5.9 ^c	3.9-8.3
Breast	43/41.5	1.0	0.8-1.4	40/35.6	1.1	0.8-1.5	38/17.2	2.2 ^c	1.6-3.0
Colon	30/23.3	1.3	0.9-1.8	33/17.0	1.9 ^c	1.3-2.7	22/7.9	2.8 ^c	1.7-4.2
Rectum	10/9.4	1.1	0.5-1.9	2/7.6	0.3	0.0-0.9	3/2.9	1.1	0.2-3.1
Stomach	7/8.9	0.8	0.3-1.6	3/6.4	0.5	0.1-1.4	0 ^d	—	—
Lung	10/4.9	2.0 ^c	1.0-3.8	3/4.4	0.7	0.1-2.0	3/3.6	0.8	0.2-2.4
Bladder	2/4.7	0.4	0.05-1.5	9/3.2	2.8 ^c	1.3-5.3	0 ^d	—	—
Lymphoma	6/3.7	1.6	0.6-3.5	6/2.2	2.7 ^c	1.0-5.9	6/1.7	3.6 ^c	1.3-2.8
Leukemia	1/4.0	0.25	0.01-1.4	4/3.0	1.3	0.4-3.7	15/1.6	9.3 ^c	5.2-15.3
Myeloma	4/1.4	2.8	0.7-7.1	0/1.2	—	0.0-3.1	0 ^d	—	—
Connective tissue	1/1.1	0.9	0.02-5.1	3/0.9	3.3	0.7-9.7	0 ^d	—	—

^a Observed No. of cancers/expected No. of cancers.

^b Around the estimate of RR.

^c $P \leq 0.05$.

^d Less than 2 patients observed.

and hospitals, by difficulty in differentiating metastases from second primary cancers, and by possible inclusion of occult tumors from autopsies. Although such biases must be considered, information from these surveys may provide useful clues to cancer etiology.

Our study confirmed previous reports (2, 3) that women with ovarian cancer are prone to neoplasms of the endometrium, colon, and possibly breast and for the first time evaluated the influence of previous therapy on the development of bladder cancer, lymphoma, and leukemia.

The excess of carcinoma of the uterine corpus occurred in all treatment groups in the E.R.P.. This may partly reflect uterine tumors discovered during pelvic surgery of ovarian cancer or misdiagnosed metastases, but a similar excess in the current survey of university-based gynecologic oncologists suggests a complex of tumors resulting from common etiologic (hormone?) influences. Recent reports linking endometrial and ovarian cancers (10, 11) to stilbestrol support this possibility.

Colon cancer also occurred in excess in both surveys and in all treatment groups of the E.R.P. Among nonirradiated patients the risk of colon cancer was limited to the first 2 years of follow-up, which suggests common etiologic factors or possibly ascertainment bias from abdominal surgery. An excess of ovarian cancer following colon cancer noted in the E.R.P. (Reimer RR, Hoover R: Unpublished observation) and in a single institution survey (12) also suggests that these 2 neoplasms may result from common etiologic influences. After radiotherapy, the risk for colon cancer was elevated among patients followed longer than 5 years. This finding is consistent with the reported excess of colon and rectal carcinomas in patients irradiated for benign gynecologic conditions (13, 14) and ankylosing spondylitis (15).

The excess of breast cancer in the current survey group is difficult to interpret. A similar excess was noted in one follow-up study of ovarian cancer patients (3) but not in another (2). Although this discrepancy may result from difficulty differentiating these 2 tumors, common etiologic factors could be involved.

A predisposition to bladder cancer was limited to irradiated patients in the E.R.P. survey, a finding consistent with that for women irradiated for benign gynecologic conditions (16).

Lymphomas occurred in excess in both surveys, particularly among irradiated patients. Although radiotherapy has not been linked to lymphoma, survivors of the atomic bomb (17) and radiologists (18) are prone to this tumor. The relationship may be mediated by immunosuppression as suggested by the high rate of lymphoma in renal transplant recipients (19).

The excess of acute nonlymphocytic leukemia among patients receiving alkylating agent therapy may be related to the capacity of these drugs to cause chromosome instability and breakage (9). Interactions with radiation therapy and/or immunosuppression may also be involved.

In summary, some primary neoplasms following

ovarian cancer appear to be influenced by common etiologic factors (endometrial and breast cancers), by therapy (bladder cancer, lymphoma, and leukemia), or by a combination of these factors (colon cancer). Delineation of the mechanisms responsible for therapy-related tumors will require further follow-up surveys of patients receiving various treatment modalities and a more detailed understanding of the interrelationships of chemotherapeutic drugs, radiation, and immunosuppression. No patient with a fatal illness such as advanced ovarian cancer should be denied potentially curative or palliative therapy for fear of developing a second cancer, but the benefit of such therapy in nonmalignant disorders or in tumors where long-term survival is likely will have to be balanced against the risks of long-term sequelae.

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